A REVIEW ON IN-SITU NASAL DRUG DELIVERY

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ABSTRACT- Numerous medications have demonstrated in recent years that nasal delivery produces greater systemic bioavailability than oral treatment. Because the concentration time profile of medications acquired following nasal administration is frequently comparable to that obtained after intravenous injection, with a consequently rapid onset of pharmacological activity, it is an appealing strategy for the systemic distribution of drugs. This review includes the mechanism of nasal drug delivery, nasal drug delivery barriers, Nasal cavity anatomy and physiology, factors impacting the absorption of nasal drug, Present Strategies for Improving Nasal Permeation.

KEY WORDS- In-situ nasal drug delivery, mechanism of nasal drug delivery, nasal drug delivery barriers, nasal cavity anatomy and physiology, factors impacting the absorption of nasal drug.

INTRODUCTION-

In the Indian Ayurvedic medical system, intranasal administration of therapy has been recognized as a legitimate treatment modality. Numerous medications have demonstrated in recent years that nasal delivery produces greater systemic bioavailability than oral treatment[1]. Many protein and peptide drugs are now accessible for the treatment of many ailments because to advancements in biotechnology. Due to their considerable gastrointestinal tract degradation or hepatic first-pass impact metabolism, some medications are not appropriate for oral administration. For long-term treatment, even the parenteral route is inconvenient. Out of all the other routes that have been investigated, intranasal drug delivery has shown the most promise for administering these medications[2]. Because the concentration time profile of medications acquired following nasal administration is frequently comparable to that obtained after intravenous injection, with a consequently rapid onset of pharmacological activity, it is an appealing strategy for the systemic distribution of drugs. Furthermore, intranasal delivery offers a practical way to administer medications to the central nervous system (CNS) and items with local activity. From the perspective of the pharmaceutical industry (no need to sterilize nasal preparations) and the patient (quick onset of action, noninvasiveness, essentially painless, ease of delivery, favorable tolerability profile, enhanced patient compliance, ease of convenience, self-medication), intranasal administration provides a number of useful benefits. Therefore, if the pharmacokinetic benefits of the intranasal route to overcome patient compliance are increased[3]. The nasal route of administration is appealing for many medications, including small molecular weight polar pharmaceuticals, proteins, and peptides, due to the nasal mucosa's highly supplied vascular nature and high drug penetration rate. DNA and vaccines are two examples of macromolecules that are delivered via the nasal route. Furthermore, the CNS may be able to access a pharmaceutical

component through drug absorption at the nose's olfactory area. Because intranasal delivery uses pathways along olfactory and trigeminal nerves that innervate the nasal passage, it can quickly target therapeutics directly to the central nervous system (CNS) and circumvent the blood-brain barrier (BBB) compared to invasive delivery methods like intracerebroventricular or intraparenchymal injections. When administered intranasally, the medication is quickly delivered straight from the nasal mucosa[4]. Therapeutic substances with a high molecular weight, such proteins and peptides, are prevented from penetrating the nasal mucosa. It is possible to safely and reversibly open the tight connections that make up this barrier to paracellular medication transport. Intranasal therapy is non-invasive, painless, and requires no sterile preparations. It can also be easily and quickly delivered by the patient, for example, in an emergency[5-7]. In contrast to in situ gels, liquid nasal formulations are injected into the nasal cavity as low viscosity solutions. The polymer transforms into a gel when coming into contact with the nasal mucosa. in order to gradually release medications into the nasal cavity while also lengthening the period that the drug and absorption site are in touch[8].

MECHANISM OF DRUG DELIVERY-

Drug absorption from the nasal cavity begins with passage through the mucus[9]. This layer is easily penetrated by tiny, unaltered particles. It could be more challenging for big or charged particles to cross, though. The primary protein in mucus, mucin, has the ability to attach to solutes and prevent diffusion. Environmental changes (such as pH, temperature, etc.) can also cause structural alterations in the mucus layer[10]. There are various ways for a medicine to be absorbed through the mucosa once it has passed through the mucus[11]. These consist of vesicle carrier transcytosis, paracellular transport through movement between cells, and transcellular or simple diffusion across the membrane[12]. Limited residence time in the cavity and possible metabolism prior to entering the systemic circulation are barriers to medication absorption. Although several processes have been put forth, the two methods listed below have received the most attention.

1. Aqueous transport, sometimes referred to as the paracellular pathway, is a component of the first mechanism. This path is passive and slow. Intranasal absorption and the molecular weight of water-soluble substances have an inverse log-log correlation. Drugs with a molecular weight larger than 1000 Daltons showed poor bioavailability[13].

2. The transport of lipophilic medications that exhibit a rate dependence on their lipophilicity is accomplished via the second mechanism, which involves transport via a lipoidal pathway, also referred to as the transcellular process. Additionally, drugs can move through tight junctions or an active transport pathway that involves carrier-mediated transport across cell membranes[14].

Advantages of Nasal drug delivery-

1.Self-medication is made easier by convenient accessibility and needle-free drug application without the requirement for skilled staff, which improves patient compliance as compared to parenteral approaches[15].

2. Good nasal mucosal penetration, particularly for lipophilic, low molecular weight medications. For example, fentanyl has an absolute nasal bioavailability of roughly 80%[16].

3. Because of its strong vascularization and comparatively broad absorption surface, it absorbs and acts quickly. Therefore, fentanyl's Tmax following nasal injection was less than or equivalent to seven minutes, which is comparable to intravenous [i.v.] .Therefore, nasal delivery of an appropriate medication would be a viable substitute for parenteral administration routes in emergency therapy[16].

4. Avoiding the severe environmental factors in the digestive system (chemical and enzymatic breakdown of nutrients)

5. When compared to oral delivery, the possibility for dose reduction arises from avoiding hepatic first pass metabolism.

6. The ability to bypass the blood-brain barrier and deliver a medication directly to the central nervous system through the olfactory area[17].

7. Vaccine administration directly to lymphatic tissue and elicitation of a secretory immune response at a remote mucosal site[18].

NASAL DRUG DELIVERY BARRIERS-

1. **Low levels of bioavailability-** Polar medications often have a poor bioavailability of 10% for low molecular weight medications and less than 1% for peptides like insulin and calcitonin[19]. Low membrane permeability is the primary factor preventing polar medicines, particularly those with large molecular weights like proteins and peptides, from being absorbed by the nose. There are three ways that drugs can get across the membrane of an epithelial cell: paracellularly through the narrow spaces between cells, via receptor-mediated or vesicular transport pathways, or transcellularly by taking advantage of straightforward concentration gradients. The latter method is typically used by polar medications whose molecular weights are less than 1000 Da to cross the barrier. Despite being dynamic structures that can partially open and close when necessary, tight junctions have a typical size of less than 10 Å, which significantly restricts their ability to carry bigger molecules[20]. Through an endocytotic transport mechanism, larger peptides and proteins can cross the nasal membrane, but only in trace amounts[21]. Coadministration of absorption-enhancing substances can significantly increase the nasal absorption of such polar medications[22]. Surfactants (laureth-9, sodium laurylsulfate), bile salts and bile salt derivatives (sodium glycocholate, sodium deoxycholate, sodium taurodihydrofusidate), fatty acids and fatty acid derivatives (linoleic acid),

phospholipids (lysophosphatidylcholine, DDPC), different cyclodextrins (dimethyl-}-cyclodextrin, parenteral `-, }-, and }-cyclodextrin), and cationic compounds (chitosan and derivatives, poly-L-arginine, poly-L-lysine) are among the agents commonly used for transnasal absorption[23]. There are several ways in which these enhancers function, but often they change the permeability of the epithelial cell layer by changing the phospholipid bilayers, causing proteins to leak out of the membrane, or even removing the mucosa's outer layer. Some of these enhancers also function as inhibitors of enzymatic degradation and/or have an impact on tight junctions[22].

Even for bigger peptides like insulin, higher bioavailabilities were achieved with such absorption-enhancing compounds. A direct relationship between the absorption-enhancing effect and nasal mucosal injury has been demonstrated in animal experiments for a variety of enhancing agents; this is especially true for bile salts and surfactants. The benefits of other enhancers, like chitosan and cyclodextrins, exceed the harm done to the mucosa. Therefore, while choosing an absorption enhancer for a nasally administered medication that is difficult to absorb, it is crucial to take systemic and nasal toxicity into account[24].

2. **Clearance of mucociliary**-The general quick clearance of the supplied formulation from the nasal cavity due to the mucociliary clearance mechanism is another element of importance for limited membrane transport. This is particularly true if the medication is not sufficiently absorbed through the nasal mucosa. It has been demonstrated that the half-life for clearance for non-bioadhesive liquid and powder formulations is between 15 and 30 minutes[25-26]. Using bioadhesive excipients in formulations is one way to get around the mucociliary clearance's rapidity. Placing the formulation in the nasal cavity's anterior, less ciliated region can also lower the clearance and increase absorption[27-28].
3. **Degradation of enyme-**The potential for enzymatic destruction of the molecule in the nasal cavity lumen or during passage through the epithelial barrier is another contributing, but frequently overlooked, factor to the limited bioavailability of peptides and proteins across the nasal mucosa. Both of these sites have endopeptidases like serine and cysteine that can break down internal peptide bonds and exopeptidases like mono and diaminopeptidases that can cleave peptides at their N and C termini[29]. Enzyme saturation and/or the application of enzyme inhibitors are two strategies to get beyond this obstacle[30].

Nasal cavity anatomy and physiology:

Two hales make up the nasal cavity, however the nasal vestibule is the most anterior portion and opens out through the nostril to the nose by the nasal septum and extends back to the nasopharynx .The respiratory, olfactory, and nasal vestibule are the three primary areas that make up the nose cavity. Around 150 cm of lateral nasal cavity walls, which have a folded structure, might expand the nose's surface area[31]. Its surface area is extremely large in relation to its little volume. The superior, median, and inferior turbinates make up this folded structure. The nasal airway's main tasks are aided by its tiny channels, which are between 1 and 3 mm broad. A mucous membrane that divides into non-olfactory and olfactory epithelium covers the nasal cavity. While the respiratory field, which has a typical airway epithelium loaded with numerous microvilli, offers a

sizable area accessible for drug absorption and transportation, the nasal vestibule in the non-olfactory region is lined with skin-like stratified squamous epithelial cells[32]. This causes a shift in the mucus layer's location from the nasal cavity's anterior to rare region. The atrium and nasal turbinate are shielded by the mucous membrane. Mucus is secreted by the goblet cells as mucus granules, which swell in the nasal fluid and add to the mucus layer. About 95% water, 2% mucin, 1% salts, 1% other proteins such albumin, immunoglobulin, lysozyme, and lactoferrin, and 1% lipids make up the mucus secretion. The immunological response to inhaled germs and viruses is suppressed by the mucous discharge[32].

Additionally, it carries out certain physiological tasks, which are listed below-

a) This creates the mucosa and maintains it both enzymatically and physically.

b) Mucus has the ability to retain water.

c) The surface of this shows electric activity.

d) It permits effective heat transfer.

e) In addition to acting as glue, it transports particles to the nasopharynx.

FACTORS IMPACTING THE ABSORPTION OF NASAL DRUG

A) Drug-Related Factors-

a) Lipophilicity-

With increased lipophilicity, the compound's ability to pass through the nasal mucosa usually increases.. It appears that nasal mucosae are fundamentally lipophilic in nature, and the lipid domain is vital to the membranes' barrier function, even though some hydrophilic properties have been found in them[33].

In one study, the lipophilic compounds alprenolol and propranolol were found to be well absorbed from the nasal mucosa, whereas metoprolol, a hydrophilic drug, was not.Due to their ability to partition into the lipid (bilayer) of the cell membrane and diffuse into and move through the cell in the cytoplasm, lipophilic substances have a tendency to readily penetrate biological membranes via the transcellular route. Several lipophilic medications, including testosterone, buprenorphine, and naloxone[34] and 17a-ethinyl-oestradiol[35] have been demonstrated in animal models to be fully or nearly fully absorbed through the nose. Several compounds have been used to illustrate a relationship between lipophilicity and nasal medication absorption[36].

b) Chemical Form-

A drug's chemical form can have a significant role in determining absorption. For instance, changing the drug's form to an ester or salt can change how well it is absorbed. Huang et al.[37]

examined how medication absorption is affected by structural changes. It was shown that the carboxylic acid esters of L-tyrosine had a far greater in-situ nasal absorption than L-tyrosine itself.

c) Polymorphism-

Drugs' solubility and rate of dissolution, and consequently their absorption across biological membranes, are known to be impacted by polymorphism. Therefore, research on the purity and polymorphic stability of medications for nasal powders and/or solutions is advised.

d) Molecular weight-

Whereas watersoluble compounds show an inverse connection with MW, lipophilic compounds show a direct relationship with drug penetration. Considering Fisher et al.'s[38] reports and Yamamto et al[39] that physicochemical characteristics of medications smaller than 300 Da do not greatly affect their ability to penetrate; instead, they will primarily pass through the membrane's aqueous channels. In contrast, the rate of penetration is very sensitive to molecular size for molecules with MW = >300 Da.

e) pKa and Partition Coefficient-

In terms of nasal absorption, the pH partition theory states that unionized species are better absorbed than ionized species.Jiang et al. used paracetamol and diltiazem hydrochloride as model pharmaceuticals in order to quantify the association between a drug's physicochemical characteristics and its nasal absorption. The findings demonstrated a quantitative correlation between the nasal absorption constant and the partition coefficient[40].It has been shown that the degree of ionization of weak electrolytes, such as aminopyrine and salicylic acid, greatly influences their nasal absorption. While the absorption rate for aminopyrine rose as the pH rose and was found to suit the theoretical profile well, salicylic acid showed significant deviations[41]. Similarly, when the absorption of benzoic acid was tested at pH 7.19, 10% of the drug was absorbed when 99.9% of the medication was in ionized form, indicating that the ionized species also penetrates the nasal mucosa[42].Given all of these findings, the authors concluded that partition coefficients play a significant role in nasal absorption and provided evidence that additional transport channels for hydrophilic medications may be significant.

f) Dissolution Rate and Solublity-

When assessing nasal absorption from powders and suspensions, drug solubility and dissolution rates are crucial variables. Before being absorbed, the particles that have been placed in the nasal cavity must disintegrate. No absorption occurs if a medicine is removed or stays in the form of particles.

g) Formulation Related Factors-

1) Formulation's Physicochemical Properties-

a) **Mucosal irritation and pH-**

The nasal surface's pH and the formulation's pH can both impact a drug's penetration. The nasal formulation should have a pH of 4.5 to 6.5 to prevent irritation of the nose[43]. It not only avoids irritation but also achieves effective medicine penetration and stops bacterial development.

b) **Osmolarity-**

Ohwaki et al. investigated how osmolarity affected rats' secretin absorption and discovered that absorption peaked at 0.462 M sodium chloride[44] due to the fact that the nasal epithelial mucosa shrank at this salt concentration.[45] This leads to structural alterations that increase the compound's penetration, which was further supported by the use of sorbitol as an osmoregulatory agent. Isotonic solutions are typically chosen for administration since the authors discovered that secretin penetration subsequently decreased[46].

c) **Viscosity**-

The time for penetration increases when the formulation's viscosity rises because it prolongs the drug's interaction with the nasal mucosa. Highly viscous formulations also change the permeability of drugs by interfering with typical processes like mucociliary clearance or ciliary beating.

B. Form of Dosage Used to Develop the Formulation-

The drug being used, the intended indication, the patient group, and, last but not least, marketing preferences all influence the dosage form choice. Below is a summary of several of these delivery systems and their salient characteristics.

a) **Nasal Drops-** One of the simplest and most practical devices created for nasal distribution is the nasal drop. This system's primary drawback is its lack of dose precision, which means nasal drops might not be appropriate for prescription medications. Human serum albumin has been found to be more effectively deposited in the nostrils by nasal drops than by nasal sprays[47].

b) **Nasal Sprays-** Nasal sprays can be made from both solution and suspension compositions. Metered dose pumps and actuators have made it possible for nasal sprays to precisely administer doses ranging from 25 to 200 liters. Pump and actuator assembly selection is based on formulation viscosity, drug particle size and shape (for suspensions), and both. Sprays that dissolve and suspend are better than those that employ powder since the latter causes irritation of the mucosa[48].

c) **Nasal Gels-**Thickened liquids or suspensions with a high viscosity are called nasal gels. This method did not garner much attention until the advent of accurate dosage devices. A nasal gel can reduce anterior formulation leakage, reduced post-nasal drip from high viscosity, reduced taste impact from reduced swallowing, reduced irritation from calming/emollient excipients, and targeted delivery to mucosa for better absorption[49].

Present Strategies for Improving Nasal Permeation-

The bioavailability of medications taken via the nasal route is mainly restricted due to low drug solubility, quick mucociliary clearance, weak membrane penetration, and rapid enzymatic degradation in the nasal cavity. There are other approaches that have been proposed to get around those restrictions. The following lists and explains these techniques.

Prodrugs-

Because lipophilic medicines are poorly soluble in water, they can easily cross biomembranes. Prodrugs with a higher hydrophilic character should be used to facilitate the development of an aqueous nasal formulation likely at the right concentration. When the prodrugs enter the bloodstream, they must quickly transform into the parent medication. The development of suitable nasal formulations is made possible by the fact that many L-Dopa prodrugs are more soluble than the parent medication[50-52].

Co-solvents-

Another strategy for prodrugs is the use of cosolvents to improve drug solubility. Glycerol, ethanol, propylene glycol, and polyethylene glycol are the cosolvents typically found in intranasal formulations; they may be the most important because they are non-toxic, safe to use in pharmaceuticals, and do not irritate the nasal mucosa[50].

Inhibition of enzyme-

During nasal medicine distribution, the nasal mucosa layer serves as an enzymatic barrier due to its diverse array of enzymes.. Various techniques, such as protease and peptidase inhibitors, are employed to prevent enzymatic breakdown. The breakdown of calcitonin bestatine, comostate amylase, leupeptin, and aprotinin, for instance, is inhibited by amino peptidases, which are likely tyrosine inhibitors. Moreover, puromycin, bacitracin, amastatin, boroleucin, and leucine encephalin have been used to aid stop the enzymatic breakdown of medications[53-54]. Bile salts and fluidic acid are examples of absorption enhancers that can eventually be used to accomplish the enzymatic reduction.
An absorption enhancer called disodium EDTA has been demonstrated to reduce the enzymatic breakdown of beta-sheet breaker peptide, which is used to treat Alzheimer's disease[55].

CONCLUSION-

Due to the widespread interest in intranasal mucosal administration, which offers a non-invasive, needle-free way to target the blood-brain barrier and circumvent hepatic first-pass metabolism while delivering the medication to the brain, this study was carried out. This technique offers advantages including patient comfort and compliance, less exposure, and fewer adverse effects by enabling medication administration directly to the central nervous system (CNS) via the olfactory pathway through the mucosa. The market potential of intranasal formulations is expected to be realized.

There are numerous factors which affect the absorption such as lipophilicity, polymorphism as well the type of nasal formulation.

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